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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/549,695	05/26/2006	Yasuhiko Tabata	3691-0122PUS1	9610

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EXAMINER	
SASAN, ARADHANA	

ART UNIT	PAPER NUMBER
1615	

NOTIFICATION DATE	DELIVERY MODE
12/10/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/549,695	TABATA, YASUHIKO	
	Examiner	Art Unit	
	ARADHANA SASAN	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 August 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-6* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 3-6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application

1. The remarks filed on 08/31/09 are acknowledged. There were no claim amendments.

2. Claims 1 and 3-6 are included in the prosecution.

MAINTAINED REJECTIONS:

The following is a list of maintained rejections:

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 1, 3 and 5-6 **remain** rejected under 35 U.S.C. 102(b) as being anticipated by Tabata et al. (Advanced Drug Delivery Reviews 31 (1998) 287-301).

The claimed invention is a sustained-release preparation which comprises a drug and a gelatin hydrogel. The drug is impregnated into the gelatin hydrogel through a surface thereof and is maintained in the hydrogel by physiochemical interaction. A concentration gradient of the drug is formed in the hydrogel, the concentration gradient being higher at the surface than in other parts of the hydrogel. The sustained-release preparation is sterile.

Tabata teaches that “when mixed with positively or negatively charged gelatin, an oppositely charged protein will ionically interact to form a polyion complex” (Abstract).

"The biodegradable hydrogel matrices are prepared by chemical crosslinking of acidic or basic gelatin and are enzymatically degraded in the body with time. The degradation is controllable by changing the extent of crosslinking, which, in turn, produces hydrogels with different water contents. The time course of protein release is in good accordance with the rate of hydrogel degradation. It is very likely that the protein drug complexed with gelatin hydrogel is released as a result of its biodegradation" (Abstract). The advantages of using a polymer hydrogel for protein release including biosafety and inertness towards protein drugs is disclosed (Page 288, right hand column). Tabata teaches that "for achieving effective protein release, it will be a key strategy to immobilize the protein drug to polymer carrier molecules constituting the hydrogel through some molecular interactions" and that "… stable bonding will occur between the oppositely charged polyelectrolytes, which will not dissociate easily" (Page 288, right hand column). Figure 1 shows protein drug release from a biodegradable polymer carrier on the basis of polyion complexation where "a positively charged protein drug is electrostatically complexed with negatively charged polymer chains, constituting a carrier matrix" (Page 289, left hand column). Biodegradable gelatin is the carrier polymer for the hydrogel (Page 289, right hand column). Preparation and sterilization of the hydrogels is disclosed (Page 290, under "Preparation of gelatin hydrogels"). Injectable shapes of the gelatin hydrogels (i.e., solids) are disclosed (Page 289, under the section "2.2 Injectable matrices"). Various proteins that are used as drugs for the polyion complexation are disclosed, including bovine milk lactalbumin and basic fibroblast growth factor (bFGF) (Page 291, under section 3.1. "Polyion complexation in

aqueous solution"). "The interaction of protein with gelatin results in protein sorption to the gelatin hydrogel" (Page 292, under section 3.2. "Interaction of protein with gelatin hydrogel"). "It may be concluded that the initial driving force of bFGF sorption to the acidic gelatin hydrogel is electrostatic interaction between the two molecules …" (Page 293, left hand column). Tabata also teaches that "gelatin hydrogels were subcutaneously implanted into the backs of mice and the weights of the hydrogels were measured at different time intervals to evaluate the time profile of in vivo hydrogel degradation" (Page 293, left hand column, and Fig. 5). In vitro release profiles of bFGF that was incorporated into a gelatin hydrogel through impregnation are disclosed (Page 294, left hand column and Fig. 6). This gelatin hydrogel system prevents the protein drug from denaturing, and the release of the protein "is governed by matrix degradation and hence, the period of protein release can be regulated by changing the rate of hydrogel degradation" (Page 298, left hand column).

Regarding instant claim 1, the limitation of a sustained-release preparation which comprises a drug and a gelatin hydrogel is anticipated by the sustained release of bFGF from gelatin hydrogels, as taught by Tabata (Abstract, Page 288 - right hand column, Page 298 - left hand column). The limitation of the drug that is impregnated into the gelatin hydrogel through a surface thereof is anticipated by the bFGF that was incorporated into a gelatin hydrogel through impregnation, as disclosed by Tabata (Page 294, left hand column and Fig. 6). The limitation of maintaining the drug in the hydrogel by physiochemical interaction is anticipated by the ionic interaction of drug and polymer to form a polyion complex, as taught by Tabata (Abstract and Page 291, under

section 3.1. “Polyion complexation in aqueous solution”). The limitation of a concentration gradient of the drug in the hydrogel, the concentration gradient being higher at the surface than in other parts of the hydrogel is anticipated by the release of drug from the gelatin hydrogel as a result of its biodegradation, as taught by Tabata (Abstract). Since the protein drug is applied on the surface of the gelatin hydrogel, the concentration of the drug will intrinsically be higher on the surface. The limitation of the sterile sustained-release preparation is anticipated by the sterilization of gelatin hydrogels, as taught by Tabata (Page 290, under “Preparation of gelatin hydrogels”).

Regarding instant claim 3, the limitation of a method of sustained release of a drug in vivo comprising administering a sustained-release preparation to a patient in need thereof is anticipated by the in vivo release of bFGF from the gelatin hydrogel, as taught by Tabata (Page 294, right hand column and Page 295, right hand column). The limitation of degradation of gelatin hydrogel in vivo causing more drug to be released from a region of higher drug concentration is anticipated by the release of bFGF from the gelatin hydrogel as a result of hydrogel degradation, as taught by Tabata (Page 294, right hand column). The limitation of the maintenance of the drug in the hydrogel by a physiochemical interaction is anticipated by the polyion complexation, as taught by Tabata (Abstract and Page 291, under section 3.1. “Polyion complexation in aqueous solution”). The limitation of a concentration gradient of the drug in the hydrogel, the concentration gradient being higher at the surface than in other parts of the hydrogel is anticipated by the release of drug from the gelatin hydrogel as a result of its biodegradation, as taught by Tabata (Abstract). Since the protein drug is applied on the

surface of the gelatin hydrogel, the concentration of the drug will intrinsically be higher on the surface. The limitation of the sterile sustained-release preparation is anticipated by the sterilization of gelatin hydrogels, as taught by Tabata (Page 290, under "Preparation of gelatin hydrogels").

Regarding instant claim 5, the limitation of drug impregnation into the gelatin by ionic bonding is anticipated by the anticipated by the bFGF that was incorporated into a gelatin hydrogel through impregnation (Page 294, left hand column and Fig. 6), and by the ionic interaction of drug and polymer to form a polyion complex, as taught by Tabata (Abstract and Page 291, under section 3.1. "Polyion complexation in aqueous solution").

Regarding instant claim 6, the limitation of the preparation in a solid form is anticipated by the injectable shapes taught by Tabata (Page 290, right hand column).

Response to Arguments

5. Applicant's arguments, see Page 2, filed 08/31/09, with respect to the rejection of claims 1, 3 and 5-6 under 35 U.S.C. 102(b) as being anticipated by Tabata et al. (Advanced Drug Delivery Reviews 31 (1998) 287-301) have been fully considered but are not persuasive.

Applicant argues that Tabata et al. fail to teach or suggest a concentration gradient of the drug. Applicant argues that "the Examiner appears to take Official Notice of the fact that the concentration gradient would be higher at the surface than in other parts of the hydrogel in view of the fact that the drug will release from the gelatin hydrogel as a result of its biodegradation. It is unclear to Applicant what basis the Examiner has for making this statement. Applicant respectfully challenges this first

assertion by the Examiner. Applicant requests that the Examiner provides documentary evidence to support the assertion that the concentration gradient would be higher at the surface than in other parts of the hydrogel in view of the fact that the drug will release from the gelatin hydrogel as a result of its biodegradation. Second, the Examiner appears to take Official Notice of the fact that the concentration of the drug will intrinsically be higher on the surface, since the protein drug is applied on the surface of the gelatin hydrogel. Again, Applicant respectfully challenges this second assertion by the Examiner. Applicant requests that the Examiner provides documentary evidence to support the assertion that the concentration of the drug will intrinsically be higher on the surface, since the protein drug is applied on the surface of the gelatin hydrogel." Applicant does not "believe that the cited reference provides any disclosure which would make one skilled in the art believe that the concentration gradient would necessarily be inherent in the hydrogel of Tabata et al."

Applicant cites Section 3.2 of Tabata et al. (Page 292) and argues that "the skilled artisan would not reasonably conclude that protein molecules which freely diffuse into the interior of a hydrogel would have a concentration gradient with a higher concentration at the surface."

This is not persuasive because claim 1 is a product-by-process claim, which is considered a product claim by the Office. Applicants are reminded that process limitations cannot impart patentability to a product that is not patentably distinguished over the prior art. In *re Thorpe et al.* (CAFC 1985), supra; In *re Dike* (CCPA 1968) 394 F2d 584, 157 USPQ 581; Tri-Wall Containers, Inc. v. United States et al. (Ct Cls 1969)

408 F2d 748, 161 USPQ 116; In re Brown et al. (CCPA 1972) 450 F2d 531, 173 USPQ 685; Ex parte Edwards et al. (BPAI 1986) 231 USPQ 981.

It is not clear if the “concentration gradient of the drug" is present during the method of preparing the drug-impregnated gelatin hydrogel or if the “concentration gradient of the drug" is achieved during the release of the drug from the gelatin hydrogel. It is the Examiner’s position that the “concentration gradient of the drug" is present when the drug is being released from the gelatin hydrogel. When the drug is embedded in the gelatin hydrogel, the drug will travel from the center of the gelatin hydrogel to the surface in order to be released. As the drug is being released, the directionality will be from the area of high drug concentration to an area of lower drug concentration, thereby forming a “concentration gradient of the drug.” Tabata teaches sustained release of bFGF from gelatin hydrogels (the bFGF was incorporated into the gelatin hydrogel through impregnation) (Abstract, Pages 288, 294, 298, and Fig. 6). Since Tabata teaches that the drug is released from the gelatin hydrogel as a result of its biodegradation, this product will inherently form a “concentration gradient of the drug" as the drug is being released from the hydrogel.

Moreover, a skilled artisan would recognize that if a particular concentration of drug (for e.g., 1M) is incorporated into a gelatin hydrogel (following the teaching of Tabata), there will only be one concentration of drug throughout the gelatin hydrogel (i.e., 1M). It is only when the drug is being released from the surface of the gelatin hydrogel to the outer milieu that a concentration gradient of the drug will develop, i.e.,

higher concentration of drug inside the hydrogel and lower concentration of drug outside the hydrogel.

Therefore, the rejection of 04/29/09 is maintained.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claim 4 **remains** rejected under 35 U.S.C. 103(a) as being unpatentable over Tabata et al. (Advanced Drug Delivery Reviews 31 (1998) 287-301) in view of Ueda et al. (US 4,749,574).

The teaching of Tabata is stated above.

Tabata does not expressly teach topical administration of the drug-gelatin hydrogel sustained release preparation.

Ueda teaches sustained release transdermal delivery preparations with skin-compatible bases including hydrogels comprised of water-soluble high polymers like gelatin (Col. 2, lines 30-49).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a sustained release preparation of a drug impregnated in a gelatin hydrogel, as suggested by Tabata, combine it with the transdermal delivery preparation of a gelatin hydrogel, as taught by Ueda, and produce the instant invention.

One of ordinary skill in the art would do this because the use of gelatin hydrogels in administering actives across the skin is known in the art, as evidenced by Ueda (Col. 2, lines 30-49). Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results would have been obvious. Please see MPEP 2141.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Regarding instant claim 4, the limitation of the topical administration would have been obvious over the use of gelatin hydrogels in administering actives across the skin is known in the art, as taught by Ueda (Col. 2, lines 30-49).

Response to Arguments

8. Applicant's arguments, see Page 2, filed 08/31/09, with respect to the rejection of claim 4 under 35 U.S.C. 103(a) as being unpatentable over Tabata et al. (Advanced Drug Delivery Reviews 31 (1998) 287-301) in view of Ueda et al. (US 4,749,574) have been fully considered but are not persuasive.

Applicant argues that "in view of the fact that Ueda et al. fail to cure the deficiencies of Tabata et al., a *prima facie* case of obviousness cannot be said to exist."

This is not persuasive because as discussed above, the "concentration gradient of the drug" is an inherent feature of the drug incorporated gelatin hydrogel. Ueda is

used as a supporting reference to remedy the deficiency of topical administration of the drug-gelatin hydrogel sustained release preparation. Ueda is properly combined by Tabata because the use of gelatin hydrogels in administering actives across the skin is known in the art, as evidenced by Ueda (Col. 2, lines 30-49). Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results would have been obvious. Please see MPEP 2141.

Therefore, the rejection of 04/29/09 is maintained.

Conclusion

9. No claims are allowed.

10. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Aradhana Sasan whose telephone number is (571) 272-

9022. The examiner can normally be reached Monday to Thursday from 6:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert A. Wax, can be reached at 571-272-0623. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Aradhana Sasan/
Examiner, Art Unit 1615

/Robert A. Wax/
Supervisory Patent Examiner, Art Unit 1615